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ORIGINAL ARTICLE

Chest Pain Relieved with a Bronchodilator or Other Asthma Drugs

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ABSTRACT

Background: Although many patients who experience chest pain or pressure consult their physicians, unfortunately a large number of them do not, and consequently they remain undiagnosed and untreated. Chest pain, in a subset of these patients, may be relieved with a bronchodilator or other asthma drugs.

Methods: This retrospective study included twenty cases of chest pain that were relieved with asthma drugs. Chest pain was categorized into three types: chest pain variant asthma, bronchial asthma with chest pain, and non-asthmatic allergic chest pain. Chest pain variant asthma was defined as chest pressure that improved in response to a bronchodilator, without the characteristic attacks of bronchial asthma. Bronchial asthma with chest pain was defined as chest pressure, with the characteristic attacks of bronchial asthma that improved following the administration of a leukotriene receptor antagonist, systemic corticosteroid, or bronchodilator. Non-asthmatic allergic chest pain was defined as chest pressure without the typical asthma attack, but with chest pressure that improved in response to a leukotriene receptor antagonist or systemic corticosteroid, but not a bronchodilator.

Results: Fourteen cases of chest pain were diagnosed as variant asthma, three cases were diagnosed as bronchial asthma with chest pain, and three cases were diagnosed as non-asthmatic allergic chest pain.

Conclusions: The results suggest that the mechanism underlying chest pain that is relieved with asthma drugs can involve either an airway constriction pathway or a non-constrictive pathway presumably airway inflammation. Analysis of the patient's response to treatment with asthma medication is useful for the correct diagnosis of the source of chest pain.

KEY WORDS

bronchial asthma, bronchodilator, chest pain, leukotriene receptor antagonist

INTRODUCTION

Many patients who experience chest pain consult physicians and are usually diagnosed as having respiratory (pneumothorax, pleuritis, pulmonary embolism, etc.), coronary (myocardial infarction, angina pectoris, etc.), or gastrointestinal (reflex esophagitis, gastric ulcer, etc.) diseases. However, many patients remain undiagnosed.

There are several reports of chest pain variant asthma as a variant form of bronchial asthma.[1-7] This condition presents with chest pressure that improves in response to treatment with a bronchodilator. However we have found cases with chest pressure who improved following the administration of a leukotriene receptor antagonist, but not a bronchodilator, inconsistent with the feature of chest pain variant asthma. Therefore, a subset of patients with chest pain of unknown origin can be successfully treated with the use of a bronchodilator or other asthma drugs. Since chest pain which improves following the administration of asthma drugs is relatively uncharacterized, we examined twenty cases of such chest pain and propose new clinical entities other than chest pain variant asthma.

METHODS

Twenty patients diagnosed with chest pain that was

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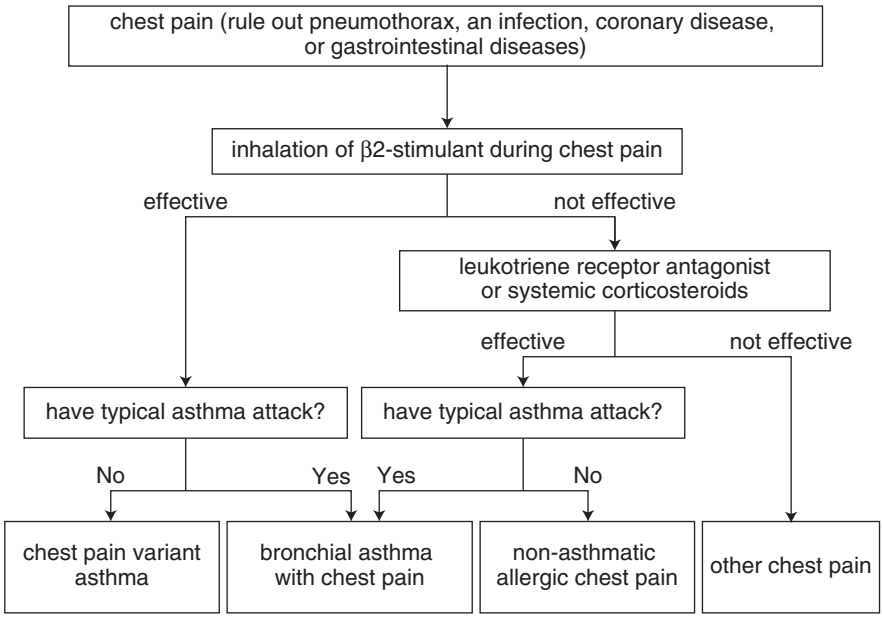

Fig. 1 Schematic algorithm to treat patients with chest pressure of unknown etiology.

relieved with the use of asthma drugs at the Toyama Prefectural Central Hospital between November 2006 and March 2008 were studied retrospectively. The primary complaints of all patients included chest pressure. Most patients received a chest X-ray, laboratory diagnostics, an electrocardiogram, sublingual administration of nitroglycerin, and an upper gastrointestinal endoscopy to verify that they were not suffering from pneumothorax, an infection, coronary disease, or gastrointestinal diseases. Patients received a bronchodilator (0.03 mg of procaterol hydrochloride, a short acting β2-stimulant) via inhalation during chest pain. If no change in the symptom was observed after inhalation, we administered a cysteinyl leukotriene receptor antagonist (10 mg/day of montelukast) for a week. If no change in the symptoms was observed after the administration of a cysteinyl leukotriene receptor antagonist, we then administered a systemic corticosteroid (approximately 0.4–0.5 mg/kg/day of prednisolone) for a week. The patients were given a diagnosis following a positive response to the inhalation of a bronchodilator or a cysteinyl leukotriene receptor antagonist or a systemic corticosteroid (Fig. 1).

The twenty patients were placed into three categories: "chest pain variant asthma," "bronchial asthma with chest pain," and "non-asthmatic allergic chest pain". There are no clear diagnostic criteria established for chest pain variant asthma,[3] but it is defined here as chest pressure (without the characteristic attacks of bronchial asthma) that improves in response to treatment with a bronchodilator. Cases that presented with the characteristic attacks of bronchial asthma with chest pressure that improved following the administration of a leukotriene receptor antagonist, systemic corticosteroid, or bronchodilator were defined as bronchial asthma with chest pain. We defined the characteristic asthma attack as recurrent episodes of wheezing and breathlessness, which are reversible either spontaneously or with treatment. Cases presenting without an asthma attack but having persistent or recurrent chest pressure that improved in response to a leukotriene receptor antagonist or systemic corticosteroid, but not a bronchodilator, were defined as non-asthmatic allergic chest pain. This study was approved by the ethics committee at the Toyama Prefectural Central Hospital.

RESULTS

The twenty cases of chest pain relieved with asthma drugs are summarized in Table 1–4. Fourteen cases were diagnosed as chest pain variant asthma, three were diagnosed as bronchial asthma with chest pain, and three were diagnosed as non-asthmatic allergic chest pain (Table 1). The average age at onset of chest pain was 36.1 years, and the male : female sex ratio was 1 : 1. Fluoroenzymeimmunoanalyses (UniCAP®) specific immunoglobulin E studies were performed in seventeen patients, nine of whom were positive.

The primary complaints from the patients included substernal pressure in thirteen patients and deep inspiration-induced chest pressure in four patients (cases 4, 8, 9, and 17). Interestingly, case 3 experienced right head pressure in association with right chest pressure. Only two cases (cases 5 and 8) reported dyspnea in association with the chest pressure attacks.

Table 1 Characteristics of chest pain relieved with asthma drugs in twenty patients (1)

No.	Sex	Age of onset	Age of diagnosis	Serum IgE (IU/ml)	UniCAP specific IgE †	Past history	Chief complaints	Aspects of chest pain attack
(chest pain variant asthma)								
1	M	37	37	7,365	+	atopic dermatitis	substernal pressure, chest discomfort	lasted from 2 hours to half a day in the morning
2	M	24	24			childhood asthma	substernal pressure	induced by smoking, lasted 15 minutes, a few times a day
3	M	34	37				substernal and right chest pressure, headache	severe pain lasted 5 minutes, and mild pain around it
4	M	47	47	29	-		substernal pressure induced by deep inspiration, dyspnea	severe pain lasted 5 minutes, a few times a day
5	F	32	32	48	-		substernal pressure, dyspnea	lasted all day, severe pain
6	M	40	62	91	-		substernal pressure	lasted 20 minutes in the morning, once a few days
7	F	58	58	10	-		substernal pressure	lasted all day, severe pain
8	M	17	17	440	+	childhood asthma	right chest pressure induced by deep inspiration, dyspnea	lasted all day
9	M	17	17	793	+		left chest pressure induced by deep inspiration	lasted all day
10	M	30	30	93	-	allergic rhinitis	left chest pressure, cough	lasted for a few hours, a few times a day
11	F	71	71	17	-		right chest pressure	lasted all day
12	F	20	81	313	+		right chest pressure	lasted an hour, many times a day
13	F	66	66				upper chest and throat pressure	lasted all day
14	F	16	25	13	+		substernal pressure	lasted a minute, a few times a month
(bronchial asthma with chest pain)								
15	F	23	27	123	+	bronchial asthma	substernal pressure	lasted from half an hour to all day
16	M	74	74	15	-	bronchial asthma	left upper chest pressure	lasted all day
17	M	29	29	926	+	bronchial asthma	substernal pressure induced by deep inspiration	lasted all day
(non-asthmatic allergic chest pain)								
18	F	17	17	250	+	childhood asthma	substernal pressure	lasted all day
19	F	47	47	4	-	sarcoidosis	substernal pressure	lasted all day
20	F	26	29	142	+		substernal pressure	lasted a few seconds, many times a day

† UniCAP specific IgE, Fluoroenzymeimmunoanalyses specific immunoglobulin E.

Three patients (cases 15, 16, and 17) were previously diagnosed with bronchial asthma, and three patients (cases 2, 8, and 18) had a history of childhood asthma. Other patients were suffering from atopic dermatitis (case 1), allergic rhinitis (case 10), and sarcoidosis (case 19). Two patients (cases 1 and 6) experienced chest pain attacks only in the morning, while five patients (cases 3, 4, 10, 12, and 20) experienced pain at various times throughout the day. Smoking induced attacks were observed in two pa-

Table 2 Characteristics of chest pain relieved with asthma drugs in twenty patients (2)

No.	Typical asthma attack	Dyspnea attack without wheezing	Wheezing during chest pain attack	Flow volume curve pattern at first examination	Bronchodilator test at chest pain			Change in the pulmonary function between the initial phase and the stable phase after treatment	
					Change of chest pain	Change in FEV_1 †	Change in PEF ‡	Change in FEV_1 †	Change in PEF ‡
(chest pain variant asthma)									
1	-	-	-	normal	disappeared	0%	0%		
2	-	-	-	obstruction	disappeared	10%	0%	-7%	-2%
3	-	-	-	severe central airway obstruction	disappeared	-2%	44%	0%	45%
4	-	-	-	obstruction	improved	4%	6%	12%	15%
5	-	-	-	severe central airway obstruction	disappeared	3%	6%	55%	211%
6	-	+	-	severe central airway obstruction	disappeared				
7	-	-	-	severe central airway obstruction	improved	impossible for chest pain			
8	-	-	-	mild central airway obstruction	disappeared	6%	23%	-4%	48%
9	-	-	-	normal	improved	3%	-3%		
10	-	-	-	mild central airway obstruction	disappeared	8%	28%		
11	-	-	-	severe obstruction	disappeared	11%	51%		
12	-	-	-	severe obstruction	improved	18%	9%		
13	-	-	-	normal	disappeared	14%	28%		
14	-	-	-	normal	disappeared	4%	0%		
(bronchial asthma with chest pain)									
15	+	-	-	obstruction	no change				
16	+	-	-	severe obstruction	no change				
17	+	-	-	normal	no change	7%	14%		
(non-asthmatic allergic chest pain)									
18	-	-	-	normal	no change				
19	-	-	-	mild central airway obstruction	no change				
20	-	-	-	normal	no change				

† FEV_1, forced expiratory volume in one second.

‡ PEF, peak expiratory flow.

tients (cases 2 and 10). The duration of chest pain varied from a few seconds to months, and the level of pain varied from mild to severe and immobilizing. Two patients (cases 4 and 6) had attacks of dyspnea with no wheezing that were not related to the chest pain attacks. None of the patients showed signs of wheezing during the chest pain attacks.

Inhalation of a short-acting β2-stimulant improved the chest pain attacks in fourteen patients; there was no improvement in the remaining six patients (Table 2). Interestingly, treatment of five patients with a bronchodilator, steroids, and leukotriene receptor an-

Table 3 Measurement of bronchial hyperresponsiveness to histamine in seven patients with chest pain variant asthma

No.	$PD_{20}FEV_1$	Symptom induced by test
5	264 mcg	chest pressure
7	118 mcg	chest discomfort
8	3,632 mcg	no symptom
9	6,526 mcg	chest pressure
10	1,779 mcg	no symptom
11	4,981 mcg	no symptom
13	more than 20,000 mcg	chest pressure

tagonist therapy, all had a greater effect on the peak flow rate than on the forced expiratory volume in one second (cases 3, 5, 8, 10, and 11). In addition, many chest pain variant asthma patients showed a central airway obstruction pattern during their chest pain attacks that improved after treatment with a bronchodilator. The chest pain attacks improved in two patients (cases 1 and 9) after the inhalation of a bronchodilator, although there was no change in the pulmonary function tests conducted before and after the inhalation of the bronchodilator. In case 3, the right head pressure during an attack was due to the radiation of chest pain; the head pressure was relieved after the inhalation of a bronchodilator.

Measurements of bronchial hyperresponsiveness to histamine[8] were carried out in seven patients with chest pain variant asthma; six patients tested positive (Table 3). The bronchial hyperresponsiveness tests induced chest pain attacks in three patients (cases 5, 9, and 13) and chest discomfort in one (case 7). Nonsteroidal anti-inflammatory drugs were effective against chest pain for several hours in three patients. In many patients, a leukotriene receptor antagonist provided very effective long-term control (Table 4). Indeed, leukotriene receptor antagonists are thought to be more effective than systemic corticosteroids in many patients. Inhaled corticosteroids and inhaled β2-stimulants were administered to patients with airway constrictive conditions, such as chest pain variant asthma and bronchial asthma.

DISCUSSION

The chest pain experienced by twenty patients and relieved with asthma drugs was classified into one of the following three types: "chest pain variant asthma," "bronchial asthma with chest pain," and "non-asthmatic allergic chest pain."

Whitney and co-workers[2] reported on three patients presenting with chest pain that was relieved with a bronchodilator, who were diagnosed as having asthma. This disease was termed "chest pain variant asthma," and several articles in the medical literature have now addressed this disease.[1-7] There are no clear diagnostic criteria established for chest pain variant asthma, but it should be defined as chest pain, without the characteristic attacks of bronchial asthma, that improves with the use of a bronchodilator. Challenging patients with inhalation of a bronchodilator during an attack of chest pain can be very useful in the diagnosis of this condition. In the current study, histamine inhalation challenges were performed in seven patients with chest pain variant asthma, of which six showed a positive response. Interestingly, these challenges induced chest pressure or discomfort in some patients. There is little doubt that the chest pressure was induced by constriction of the airway in the chest pain variant asthma patients; the pressure lessened in response to administration of a bronchodilator in concordance with bronchodilation and bronchoconstriction induced by histamine provoked chest pain in some patients. However the precise mechanisms of chest pain have not been elucidated. Case 13 showed a negative response to histamine inhalation challenges in spite of chest pressure. We speculate that his airway constriction after the histamine inhalation challenge was not sufficient to decrease his forced expiratory volume in one second by 20%, but was sufficient to induce chest pressure.

Bronchial asthma should be defined as reversible bronchial obstruction and airway hyperresponsiveness. The pathognomonic symptoms of this disease are reversible coughing, inspiratory wheezing, and dyspnea. Edmondstone[9] reported that patients admitted with acute asthma had experienced chest pain. Chest pain occurred in 76% of the patients examined herein, where it was characteristically observed as either a dull ache or a sharp stabbing pain in the sternal or subcostal areas. Chest pain usually occurs during asthma attacks. On occasion, patients experience continuous or repeated chest pain regardless of whether a typical asthma attack is in progression, as in cases 15, 16, and 17 in the current study.

In 1973, Farr *et al*.[10] described an asthmatic patient with chest tightness without wheezing that was relieved with a bronchodilator. This case should be diagnosed as "bronchial asthma with chest pain" because it demonstrated a typical asthma attack. The chest pressure in this case was likely induced by the constriction of the airway, since the chest pressure was reduced (improved) after administration of a bronchodilator. In the current study, three cases showed bronchial asthma with chest pain. These three patients experienced a typical asthma attack with wheezing on some occasion. However their chest pressure was not induced by increased constriction. Their chest pressure was not induced due to increased constriction of the airway, because it was not reduced (improved) in response to the bronchodilator in contrast to the report by Farr *et al*. However, the chest pressure in these three patients was induced via an allergic or other mechanisms related to leukotrienes, because the pressure was improved

Table 4 Treatment of chest pain with asthma drugs in twenty patients

No.	Long term control drug					NSAID for chest pain
	OCS	ICS	LTRA	LABA	THEO	
(chest pain variant asthma)						
1		O	O			
2		O				
3		O				
4		O	O			
5		O	O		O	effective
6	O	O		O	O	
7	O	O	O	O		effective
8		O				
9		O	O			
10		O				
11		O	O			
12		O	O			
13		O	O			
14		O				
(bronchial asthma with chest pain)						
15	O	O	O	O	O	effective
16	O	O	O	O	O	
17		O	O			
(non-asthmatic allergic chest pain)						
18	O		O			
19			O			
20			O			

LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroids; OCS, oral corticosteroids; THEO, theophylline; LABA, long-acting beta 2-adrenergic agonists; NSAID, non-steroidal anti-inflammatory drug.

by the administration of a leukotriene receptor antagonist. This suggests that the chest pain associated with bronchial asthma can occur via two pathways: a pathway involving airway constriction or a pathway involving a non-constriction mechanism. The fact that a leukotriene receptor antagonist is more effective for chest pain than other asthma drugs suggests evidence in support of the latter mechanism.

There was another group of chest pain that lasted all day and was relieved with a leukotriene receptor antagonist or systemic corticosteroid, but not with a bronchodilator. These three patients did not have either bronchial asthma or chest pain variant asthma. Their chest pressure may have been induced by allergic mechanisms, or other mechanisms involving leukotrienes, but it was not associated with constriction of the airway. This condition was defined herein as "non-asthmatic allergic chest pain", although it is possible that there are exceptional cases with non-allergic mechanisms. A leukotriene receptor antagonist is very effective in treating chest pain in patients with non-asthmatic allergic chest pain, in contrast to other asthma drugs, such as systemic corticosteroids.

The mechanism underlying the development of chest pain that can be relieved with asthma drugs is unclear at this time; it may be induced either by an airway constriction mechanism or by a non-constriction pathway, as mentioned previously. Edmondstone[9] speculated that the mechanism of chest pain related to asthma attacks is of musculoskeletal origin, but we suspect that the current cases with continuous or repeated chest pressure developed chest pain through other mechanisms. A pulmonary function test performed during the pain attack in five patients (cases 3, 5, 8, 10, and 11) with airway constriction showed a severe central airway obstruction pattern that improved with the use of the bronchodilator.[4] In these cases, the chest pain was induced in the comparatively large airways, such as the trachea.[4] As such, the patients with chest pain associated with an airway constriction pathway showed no wheezing during the chest pain attack, and many of them showed substernal pain. In two patients (cases 1 and 9), a pulmonary function test, performed during the attack, showed no significant changes after the use of the bronchodilator. The constriction on the large airways would be too weak to be reflected in the pulmonary function test. Patients suffering from chest pain with airway constriction and without airway constriction show similar symptoms. Changes in the pulmo-

nary function between the initial phase and the stable phase after a few months of treatments are important because airflow obstruction is sometimes observed, as shown case 5. It is difficult to distinguish between these two types of chest pain symptomatically. Therefore, it is possible that the two pathways are associated with the same airways and components of the nervous system. We speculate that the cause of chest pain without airway constriction involves inflammation of the airways, and that leukotrienes are associated with this pathway.

Chest pain variant asthma could be associated with chronic inflammation in the airway and corresponding airway constriction. Patients with chest pain variant asthma should be treated in the same manner as those with typical asthma.[4-7] Patients with bronchial asthma with chest pain should also be treated in the same manner as those with typical asthma, but we recommend the addition of a leukotriene receptor antagonist. It is possible to treat patients with non-asthmatic allergic chest pain with only a leukotriene receptor antagonist; this may be sufficient to control chest pain. However, if this treatment proves inadequate, a systemic corticosteroid should be prescribed. A subset of the chest pain variant asthma patients still presented with chest pain after treatment with a bronchodilator; their chest pain was abolished with the administration of a leukotriene receptor antagonist. This suggests that the chest pain in this subset of chest pain variant asthma patients is comprised of an airway non-constriction pathway component.

Although most patients who experience chest pain consult physicians, many of them remain undiagnosed. Almost half of the patients in the current study were diagnosed by other physicians as having variant angina, psychogenic problems, esophageal reflex, or cramps of the intercostal muscles. Chest pain variant asthma and bronchial asthma with chest pain are difficult to diagnose because they are poorly characterized diseases. In addition, non-asthmatic allergic chest pain is a novel condition. Chest pain that was relieved with asthma drugs has been diagnosed in twenty patients at the Toyama Prefectural Central Hospital, indicating that this clinical condition is not uncommon. Treatment with a bronchodilator and a leukotriene receptor antagonist should be considered for patients with chest pressure of unknown etiology. Obviously, it is critical to eliminate coronary disease before inhalation of a β2-stimulant. There is an apparent need for increased dissemination of knowledge concerning the chest pain that is relieved with asthma drugs.

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